Jeffrey Taylor/DC/USEPA/US
12/13/2006 03:24 PM

To NCIC HPV@EPA,
cc Walter Cybulski/DC/USEPA/US@EPA
bcc
Subject AR201 – Revision/Update to IACM's CAS# 1934-21-0

The message below pertains to revisions/updates to 2 Flavor and Fragrance HPV Consortia (FFHPVC) submissions and 4 International Association of Color Manufacturers (IACM) submissions. However, since both of the FFHPVC submissions and 3 out of the 4 IACM submissions have already been processed by EPA, the only attachment that remains is for FD&C Yellow No. 5 Food Colorant.

Jeffrey Taylor

Jeffrey A. Taylor
U.S. Environmental Protection Agency
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Chemical Control Division
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-----Forwarded by Walter Cybulski/DC/USEPA/US on 11/07/2006 04:56PM -----

To: Walter Cybulski/DC/USEPA/US@EPA
From: Tim Adams <tadams@therobertsgroup.net>
Date: 11/07/2006 02:12PM
Subject: RE: HPV Challenge Program Submission Inquiry Letters

Dear Walt: I appreciate your updating me on the status of our (IACM and FFHPVC) on the EPA comments on our test plans for the C6-C10 Aliphatic Aldehydes Category and the Monoterpene Hydrocarbons Category. I thought it would be worthwhile to keep you informed of where we are in the finalization of test plans and robust summaries and the responses to EPA comments on all categories we are responsible for.

Below is a list of chemical category or single substance responses to EPA comments, revised test plans and robust summaries that have been recently submitted to the EPA website on or prior to November 7, 2006. I have attached a copy of the response letter for each chemical category or chemical we have recently completed. Our intention is to complete all submissions by December 31, 2006.

1. Monoterpene Hydrocarbons (FFHPVC)
2. Bicyclic Terpene Hydrocarbons (FFHPVC)
3. FD & C Red No. 40 -food colorant (IACM)
4. FD & C Yellow No. 5-food colorant (IACM)
5. FD & C Sunset Yellow (Yellow No. 6)-food colorant (IACM)
6. Color Intermediates (Sulfanilic Acid and p-Cresidine Sulfonic Acid)(IACM)

I will keep you in the loop when we submit revised test plans, robust summaries, and responsed to EPA for the four remaining FFHPVC chemical categories.

Please contact me by email or phone with any comments yoou may have.
Regards,
Tim Adams, Ph.D.
Technical Contact for FFHPVC and IACM

-----Original Message-----
From: Cybulski.Walter@epamail.epa.gov
[mailto:Cybulski.Walter@epamail.epa.gov]
Sent: Thursday, November 02, 2006 8:36 AM
To: Tim Adams
Subject: HPV Challenge Program Submission Inquiry Letters

Mr. Adams,

I have been attempting to contact you back regarding the letters you recently received from EPA concerning chemical sponsorships under the HPV Challenge Program by two groups you represent, The Flavor and Fragrance HPV Consortia, and the International Association of Color Manufacturers.

If it is easier to contact me via e-mail with any questions you have, please feel free. In general, I noted that your letters mainly indicated that EPA had commented on submission materials for chemicals and was awaiting a reply. I examined these two cases and made the following notes indicating that your groups do appear to have replied to EPA for these categories:

> Monoterpene Hydrocarbons - Note that submission materials for this category were recently sent on 9/29/06 by FFHPVC and you indicated it was the final submission.
> C6-C10 Aliphatic Aldehydes and Carboxylic Acids - Note that

submission materials for this category are indicated as a final submssion and posted on the HPV Challenge Program website at http://www.epa.gov/hpv/pubs/summaries/alipalde/c13033tc.htm.

For the other letters you received, can you check information posted for your consortia and sponsored chemicals at http://www.epa.gov/hpv/pubs/summaries/viewsrch.htmto determine if there are any submission materials that you sent for these chemicals/catergories after EPA comments, but that may be missing from our records? If so, please forward any materials that you feel were submitted but may be absent. Otherwise, please contact me with any new information that you may have or questions that you have in relation to the letters.

Thank you.

Walter Cybulski

Walter J. Cybulski III, Ph.D.
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2006 Responses to EPA Comments on Yellow No 5.pdf

{The other attachments were removed by EPA's Jeffrey Taylor because these other attachments have already been processed by EPA. The only attachment that has not already been processed is for FD&C Yellow No. 5 Food Colorant; therefore, this attachment is found above.}

International Color Manufacturers Association
(IACM)
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Tel. (202)-293-5800 Fax (202)-463-8998

Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue N.W.
Washington, D.C. 20460

October 25, 2006

Dear Administrator:

On behalf of the International Color manufacturers Association (IACM), I wish to thank the Environmental Protection Agency (EPA) for their comments on the test plan and robust summaries on 4,5-dihydro-5-oxo-1-(4 sulfophenyl)-4-[(4-sulfophenyl)azo]-1H-pyrazole-3-carboxylic acid trisodium salt, FD&C Yellow No. 5, Tartrazine (CAS No 1934-21-0).

The IACM serves is an industry consortium to coordinate testing activities for chemical substances under the Chemical Right-to-Know Program. Since 2000, the companies that are current members of IACM have supported the collection and review of available test data, development of test plans and robust summaries, and conducted additional testing.

Based on our initial recommendations and the peer-reviewed comments of the EPA, IACM is pleased to submit the following revised test plan and robust summaries for this substance. The revised test plan and robust summaries contain additional data on existing studies and the results of additional toxicity studies that are related to the questions and comments made by the EPA in its letter dated 05/20/2005. This letter contains responses to the specific comments made by the EPA. These responses taken together with the inclusion of new study data and other information constitute the key changes to the original test plan and robust summaries.

Based on these additional data, the IACM concludes that the current test plan and robust summaries for this food color is now complete. The experimental and model data for physiochemical properties, environmental fate, ecotoxicity, and human health endpoints are consistent and provide a comprehensive basis upon which to evaluate the hazard potential of FD&C Yellow No. 5. The U.S. Food and Drug

Administration approved FD&C Yellow No. 5 for use in food (CFR 21, Part 74.340).
In an EPA letter dated 19 October 2001 concerning HPV-sponsored chemicals that are recognized as GRAS by the Food and Drug Administration, it was pointed out that:

" It may well be, on the basis of experience gained over years of use, that most of the substances have little compelling evidence suggesting that testing is needed in the context of the HPV Challenge Program. Nonetheless, while this line of reasoning could have been used to support the recommendation not to test the substances in this category, the information was only provided as background; few examples, and no actual data, were cited."

Without prior guidance from EPA, the International Color Manufacturers Association felt responsible to report endpoint data for this substance. Most of these data have already been provided to the US Food and Drug Administration during their evaluation of FD&C Yellow No. 5 as a food additive.

Based on the long history of use of FD&C Yellow No. 5 as a food additive, the hazard assessments performed by the US FDA, and the current regulatory status for the addition of this substance to the food supply, there is no compelling evidence that this substance should be further tested for physiochemical properties and human health endpoints in the EPA Chemical "Right to Know" Program. We do, however, maintain that data on the environmental fate and ecotoxicity are relevant to the HPV Challenge program. In this context, we have sponsored the collection of additional ecotoxicity data to provide a robust database on ecotoxicity endpoints. We consider that the test plan and robust summaries for FD&C Yellow No. 5 are final and have no plans to provide additional data. The EPA comprehensive comments provided the necessary guidance to complete the test plan for this category. The collaboration between the IACM and the Environmental Protection Agency in the Chemical "Right to Know" Program has produced a hazard database that will be useful to the public for decades to come. Thank you for the opportunity to participate in such a program.

If you have any questions or comments concerning the contents of this letter, please feel free to contact me at any time (202-331-2325) or tadams@therobertsgroup.net.

Best regards,

Timothy B. Adams, Ph.D.

Technical Contact Person for IACM

EPA Comments on Chemical RTK HPV Challenge Submission:
C.I. Acid Yellow 23

Summary of EPA Comments

The sponsor, the International Association of Color Manufacturers (IACM), submitted a test plan and robust summaries to EPA for C.I. Acid Yellow 23 (4,5-dihydro-5-oxo-1-(4 sulfophenyl)-4-[(4-sulfophenyl)azo]-1H-pyrazole-3-carboxylic acid trisodium salt; FD&C Yellow No. 5; Tartrazine; CAS No 1934-21-0) dated March 10, 2004. EPA posted the submission on the ChemRTK HPV Challenge Web site on March 19, 2004. Information is also provided for the proposed analogs FD&C Red No. 40, C.I. Acid Red No. 14, stilbene sulfonic acid derivatives, and FD&C Yellow No. 6 (CAS Numbers were not provided).

EPA has reviewed this submission and has reached the following conclusions:

1. Analog Justification. EPA disagrees with the submitter's proposal to use other azo dyes and stilbene sulfonic acid derivatives as representative compounds for the sponsored chemical.

Response: IACM has provided ecotoxicity data for fish and daphnia for structurally related azo dyes containing naphthalenesulfonic acid or benzenesulfonic acid substituents and carboxylic substituents. These data (LC50 >100 mg/l) confirm that azo dyes containing multiple sulfonic acid and carboxylic acid functional groups that exist in ionized form in vivo, are of low ecotoxic potential. The water solubility and other physiochemical properties including molecular weight and ionic nature under environmental conditions indicate that these compounds are not absorbed in vivo. The lack of absorption is reflected in the observed very low toxic potential for azo dyes.

2. Physicochemical Properties. The data submitted for these endpoints are adequate for the purposes of the HPV Challenge Program.

3. Environmental Fate. The submitter needs to provide measured ready biodegradation data on the sponsored chemical, include a technical discussion on stability in water in the robust summary, and provide the input values for the Level III fugacity robust summary.

Response: These data have been included.

4. Health Effects. Adequate data are available for genetic, reproductive and developmental toxicity endpoints for the purposes of the HPV Challenge Program. EPA considers acute and repeated-dose toxicity endpoints adequate on a weight-of-evidence basis. The submitter needs to address deficiencies in the robust summaries.

Response: The data have been included if available.

5. Ecological Effects. These endpoints have not been addressed adequately for the purposes of the HPV Challenge Program; the submitter needs to provide data for all

endpoints on the sponsored chemical.

Response: Four studies evaluating ecotoxicity in fish and two studies evaluating the ecotoxicity in aquatic invertebrates have been included. The azo dyes used in these studies (5-chloro-2-[(2-hydroxyl-1-naphthenyl)azo]-4-methylbenzenesulfonic acid and 2-naphthalenecarboxylic acid, [(4-methyl-2-sulfophenyl)azo], calcium salt) contain functional groups (e.g., sulfonic acid and carboxylic acids) that are responsible for the limited solubility, absorption, and toxicity of FD&C Yellow No. 5, other colors and dyes. The presence of similarly structured carbon analogs (stilbene sulfonic acid derivatives) containing sulfonic acid groups show a similar low level of ecotoxic potential.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the C.I. Acid Yellow 23 Challenge Submission

Analog Justification

The test plan provided analog data to address or support direct photodegradation, biodegradation. aquatic toxicity, and *in vivo* genetic toxicity endpoints; however, it did not provide any rationale supporting these analogs.

EPA disagrees with the submitter that the analogs proposed for the ecological effects and biodegradation endpoints are appropriate analogs for the sponsored chemical. In all the proposed analogs a distinguishing feature of the sponsored substance, the azo-linked trisubstituted pyrazole, is conspicuously absent. The proposed biodegradation endpoint analog also contains naphthyl and hydroxynaphthyl groups. The stilbene sulfonic acid derivatives proposed to supply data for the acute fish and invertebrate toxicity endpoints not only lack the azo and pyrazole functions but contain amino or nitro substituents.

Response: While we agree that the structural relatives do not contain a tri-substituted pyrazole ring, they do contain those functional groups that drive physiochemical properties and biochemical fate. The presence of ionized sulfonate and carboxylate ions under environmental conditions and in vivo conditions severely limits the absorption of these substances by biological species. Therefore, only minute amounts of these substances are available in vivo to exert a toxic effect. Due to this lack of absorption, NOAEL for studies in various species are extremely high. This has been show experimental in the absorption and metabolic studies for FD&C Yellow No. 5 and other colors and dyes containing sulfonic acid groups.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The AOPWIN data for photodegradation are adequate for the purposes of the HPV Challenge Program.

Stability in water. While EPA agrees that C.I. Acid Yellow 23 does not contain water sensitive functional groups, the submitter needs to add a brief technical discussion of this point to the robust summary.

Response: This has been more appropriately included in the test plan.

Biodegradation. The biodegradation data are not adequate for the purposes of the HPV Challenge Program The BIOWIN-estimated data are not an adequate substitute for measured data. The facts do not sustain the submitter's argument based on data from a non-standard (only 24-hr) test on proposed analog Acid Red 14 – that the test substance will not biodegrade because it does not adsorb to sludge. Although Acid Red 14 does not biodegrade under the conditions of the test, several other structurally related dyes mentioned in Shaul *et al.* 1991 are readily biodegradable but do not appear to adsorb to sludge under similar lest conditions. Measured ready biodegradation data (OECD TG 301) on the sponsored chemical are needed to address this endpoint.

Response: The several other structural relatives mentioned in the Shaul reference are not substituted with two sulfonic acid functional groups and therefore, are not good structural relatives. However, additional data has been provided on biodegradation on azo benzene sulfonic acid dyes. In all cases the model data for FD& C Yellow No. 5 and experimental data for other azo benzene and naphthalenesulfonic acid derivatives show no significant biodegradability.

Fugacity. The submitter needs to provide the input values for parameters used in the Level III estimation in the robust summaries.

Response: Input values have been included.

Health Effects (acute toxicity, repeated dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for the genetic, reproductive and developmental toxicity endpoints for the purposes of the HPV Challenge Program. EPA considers acute and repeated dose toxicity data adequate on a weight-of-evidence basis. The submitter needs to address deficiencies in the robust summaries.

Response: The data were added when if they were presented in the published or unpublished report.

Acute toxicity. Although limited data are available for this endpoint, the overall weight of evidence indicates that this endpoint has been addressed for the purposes of the HPV Challenge Program.

Repeated-dose toxicity. Data were submitted for chronic toxicity/carcinogenicity studies in rats and mice. EPA believes that on a weight-of evidence basis this endpoint has been addressed for the purposes of the HPV Challenge Program. The submitter needs to provide appropriate robust summaries for this endpoint.

Ecological Effects (fish, invertebrates, and algae)

Acute toxicity to fish, invertebrates, and algae. The submitter provided aquatic toxicity data only for chemicals that, as stated above, are not adequately similar to the sponsored chemical, or are incompletely identified (algal test). The ECOSAR values for the sponsored chemical are not appropriate because the ECOSAR model does not yet include a calculation for anionic dyes. Therefore all three acute aquatic toxicity tests following OECD Test Guidelines are needed on the sponsored chemical.

The references provided for acute fish and invertebrate toxicity in the test plan text (Greim et al., 1994) do not match those in the robust summaries. In addition, the last structure in Table 3 of the test plan does not match the name provided, 2,2'-(1,2-ethenediyl)bis(5-aminobenzenesulfonic acid), dipotassium salt (the molecular structure shows nitro substituents while the name specifies amino groups).

Response: As noted earlier, additional data has been provided to support the establishment of LC50 level for FD& C Yellow No. 5 in aquatic species. Other changes have been made as requested.

Specific Comments on the Robust Summaries

Health Effects

Repeated-dose toxicity. The submitter needs to prepare a separate robust summary for this endpoint extracting pertinent information, for the 13-week exposure duration, from the 113 week chronic toxicity/carcinogenicity studies: for example, general study information, method description, and effects on body weight, food consumption, clinical pathology findings, necropsy and histopathological findings at the earliest sacrifice interval (in this case, 1 year), NOAEL and LOAEL values, etc.

Genetic toxicity. Gene mutations. Information missing from the Ames test (Chung et al., 1981) included culture conditions (e.g. temperature and medium used), duration of incubation, number of colonies counted per concentration, the source of the metabolic activation system, responses of positive control substances, whether or not testing was conducted both with and without metabolic activation and the results for each of these test conditions.

Chromosomal aberrations. Information missing from the *in vitro* chromosomal aberrations study included culture conditions (e.g. incubation temperature), actual test concentrations, and use and response of positive control substances.

Reproductive toxicity. The robust summary for a lifetime toxicity/carcinogenicity dietary study in rats did not report pup body weight data, sex ratio of pups, estrus cycle and sperm parameters.

Developmental toxicity. Information missing from the study in rats included the proportions of fetuses examined for external, skeletal and visceral malformations, and the sex of fetuses

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.